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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/621,006	07/15/2003	Beverly L. Davidson	17023.013US2	9111

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EXAMINER	
BLUMEL, BENJAMIN P	
ART UNIT	**PAPER NUMBER**
1648	

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11/09/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/621,006	DAVIDSON ET AL.	
	Examiner	Art Unit	
	Benjamin P. Blumel	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *August 30, 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *3-9, 11-13 and 24-31* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *6,9 and 24-31* is/are rejected.

7)☒ Claim(s) *3-5,7,8 and 11-13* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *15 July 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants are informed that the rejections of the previous Office action not stated below have been withdrawn from consideration in view of the Applicant's arguments and/or amendments.

Claims 3-9, 11-13 and 24-31 are examined on the merits.

Allowable Subject Matter

The indicated allowability of claims 3-9, 11-13 and 24-31 is withdrawn in view of the newly discovered reference(s) to Chillon et al. (Genbank Accession #AAD20325, 1999). Rejections based on the newly cited reference(s) follow.

Claim Objections

Claims 3-5, 7, 8 and 11-13 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Claim 24 is objected to because of the following informalities: the recitation of "encodes nucleotides" on lines 8 and 9 of claim 24 sounds confusing since in line 5 of the same claim, the recitation of "wherein the polynucleotide encoding a chimeric Ad fiber polypeptide" is directed to amino acid sequences. Perhaps amending the claim by replacing "encodes" with "is/are" (i.e. "is SEQ ID NO: 12 or are nucleotides 1-564 of SEQ ID NO: 12). Appropriate correction is required.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

(New Rejection Necessitated by Amendment) Claims 6, 9 and 24-31 are rejected under 35 U.S.C. 103(a) as being unpatentable Kovesdi et al. (US 6,998,263), Zabner et al. (Journal of Virology, 1999), Chillon et al. (Journal of Virology, 1999), Chillon et al. (Genbank, 1999) and Davidoff et al. (Journal of Surgical Research, 1999).

The instant invention is drawn to a method of transducing a CAR lacking cell with an expression vector of an adenovirus backbone containing a chimeric Adenovirus fiber polypeptide of a tail, shaft and/or head regions encoded by: SEQ ID NO: 1, amino acids 46-188 of SEQ ID NO: l, amino acids 189-371 of SEQ ID NO: l, amino acids 1-45 of SEQ ID NO: l, SEQ ID NO: 12, nucleotides 1-564 of SEQ ID NO: 12, nucleotides 1-135 of SEQ ID NO: 12, nucleotides 136-564 of SEQ ID NO: 12. In addition the expression vector comprises a therapeutic agent and the chimeric fiber polypeptide is also operably linked to the therapeutic agent. The CAR lacking cell can be a neuronal, epithelial (HUVEC), tumor, neuroprogenitor or stem cell.

Kovesdi et al. teach the development of adenoviruses with altered cellular tropisms by producing various chimeric coat proteins (i.e. fiber, penton) by introducing nonnative viral proteins (i.e. fiber proteins with different subgroup regions combined). Kovesdi et al. teach that by altering these proteins, one in the art may generate vectors deficient in CAR binding and yet able to target and infect cells. The alteration of these proteins provides for distinct immunogenic viruses that should avoid neutralization by a humoral immune response and to provide an adenovirus selective for a potential host cell in gene therapy. The adenoviruses utilized can be from subgroups A-F, preferably, such as Ad5 or Ad30. In addition, Kovesdi et al. teach the use of these adenovirus vectors to express therapeutic agents/genes (i.e. a growth factor, a cytokine, an apoptotic agent, or an angiogenic factor, etc). However, even though Kovesdi et al. teach the importance of generating chimeric adenovirus fiber proteins to tailor the cell specific infectivity as part of gene therapy, they do not specifically state an expression vector with an adenovirus fiber protein with the amino acid residues 1-45 of SEQ ID NO: 1 or its corresponding nucleic acid bases 1-135 of SEQ ID NO: 12 or the specific target cells (HUVEC, or tumor related cells).

Zabner et al. teaches enhanced genetic transfer with an adenovirus vector comprising a chimeric fiber polypeptide. Several wild-type adenoviruses from groups A-F, were compared in the ability to infect human epithelial cells. Wild-type Ad2 (group C) was 43 times less efficient than Ad17 (group D), also a wild type. Therefore, to examine if the fiber protein of Ad17 might enhance the infection rate of Ad2 Zabner et al. compared the ability of Ad2/βgal and Ad2/Ad17/βgal, a chimeric, to infect epithelial cells. The chimeric adenovirus transferred the βgal gene more efficiently resulting in a rate of 15-95 times more βgal expression as compared to Ad2/βgal.

Chillon et al. teaches the different infection efficiencies of the multiple Adenovirus groups. Chillon et al. compared the ability of serotypes from groups A-F at infecting human umbilical vein endothelial cells (HUVEC) and central nervous system (CNS) cells. The following serotypes were used in the comparison: Ad31 of group A, Ad3, 7, and 14 of group B, Ad2 of group C, Ad9, 17, 19, 26 and 30 of group D, Ad4 of group E and Ad41 of group F. Following a 48-hour incubation period, post-infection, it was determined the adenovirus serotypes representing groups B and D had the highest rate of infection of HUVEC (20-60% and 20-90% respectively) and groups D and F infected CNS cells most efficiently (20-60% and 40% respectively). Of the least efficient serotypes to infect the target cells, Ad2 and 31 infected 5% of the CNS cells but did not infect HUVEC. The serotype able infect the highest percentage of both target cell types was Ad30, 60% for CNS cells and 90% for HUVEC. Chillon et al. further experimented with a chimeric fiber Adenovirus, testing the ability of ligating a portion of Ad17 fiber replacing most of the Ad2 fiber. A comparison was made between a chimeric Ad2βgal2(17f) and Ad2βgal2 incubating with HUVEC and CNS cells. The later proved to be 21-fold and 7-fold less efficient at transferring the βgal gene.

Chillon et al. (Genbank, 1999) teach the fiber sequence of human adenovirus 17, a group D virus, which contains amino acid residues 1-45 that are homologous to that of SEQ ID NO: 1 at positions 1-45.

Davidoff et al. teaches a method of improving an anti-tumor vaccine by altering the adenovirus vector of Ad5 with a chimeric fiber protein, which has the knob region of Ad3 and the shaft/tail regions of Ad5. This recombinant vector proved to have an increased transduction of a heterologous gene among the cancerous cell cultures when compared to the un-altered Ad5

vector. Therefore, Davidoff et al. concludes that utilizing adenoviruses chimeric fiber proteins can result in achieving optimum gene delivery *in situ* with a smaller viral dosage.

It would have been obvious to one of ordinary skill in the art to modify the method taught by Kovesdi et al. in order to transduce a CAR lacking cell with an adenovirus vector that had chimeric fiber polypeptide with either a tail, head, shaft domain or amino acids 1-45 of SEQ ID NO: 1 or nucleic acid 1-135 of SEQ ID NO: 12, thereby enhancing the administration of a therapeutic agent to a targeted cell/tissue. One would have been motivated to do so, given the suggestion by Kovesdi et al. that the modifying the coat proteins (fiber, penton) as discussed above, can improve the delivery of a therapeutic gene expressed by an adenoviral vector to a specific host cell. There would have been a reasonable expectation of success, given the knowledge that forming a chimeric fiber comprising the knob, shaft and part of the tail from Ad17 and the remainder of the tail from Ad2 provided a more efficient transfer of genes to target cells as compared with Ad2-wild type, as taught by Zabner et al., also given the knowledge that serotypes from groups B and D, particularly Ad30 and 17, offer a more efficient infectivity of HUVEC and CNS cells (cells lacking CAR) and the knowledge of the amino acids 1-45 of SEQ ID NO:1 and therefore the respective nucleic acid sequence (i.e. bases 1-135 of SEQ ID NO: 12), as taught by Chillon et al., and also given the knowledge that a recombinant adenovirus therapeutic vector with a chimeric fiber protein improved gene delivery to a series of tumor cell lines as taught by Davidoff et al. Thus the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Summary

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Benjamin P. Blumel whose telephone number is 571-272-4960. The examiner can normally be reached on M-F, 8-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell can be reached on 571-272-1600. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Benjamin P Blumel/
Examiner
Art Unit 1648

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